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Discussion: Session 1* Detection of Health Effects of Exposure to Low Doses of Agents—Scientific Constraints

The discussion opened with consideration of the suitability of animal models for extrapolation to human disease. Dr. Alarie pointed out that for some carcinogens, such as vinyl chloride, animal data had proved to be quite predictive of human effects. He commented that methods developed by Dow Chemical Company in studying uptake and excretion of several chemicals had taken account of metabolic differences between animals and man, when the human data were available. He also believes that by means of kinetic models, for at least some inhaled chemicals, it will be possible in the next few years to estimate human effects from animal data in reasonably quantitative terms. Dr. Land mentioned that for a physical agent such as ionizing radiation, animal data were useful for studying mechanisms of action.

There followed discussion of the comparability of routes of exposure. Dr. Julian Andelman (University of Pittsburgh) asked if inhalation exposure limits could give guidance to exposure limits for chemicals in water or food. There was general agreement by Drs. Esmen and Alarie that for some materials which are absorbed and metabolized in the same way, regardless of route of entry, this approach was reasonable, but in general such equivalence was not the case. For systemic toxic effects, the inhalation route could be equated to ingestion only if comparable blood levels could be established. Dr. Radford pointed out that gastrointestinal absorption involved uptake into the portal circulation, which could be very different from equivalent uptake from the lungs. Dr. Alarie agreed that biotransformations in the liver or in the blood itself may modify effects for certain rapidly metabolized chemicals such as cyanide, but for others there would be relatively little difference.

Dr. Gordon Newell (Assembly of Life Sciences, National Research Council) asked if Dr. Alarie had noted marked differences in response by different species, for example, the carcinogenic response to formaldehyde. Dr. Alarie agreed that the response to irritants was highly variable even by strain of mice. After exposure to formaldehyde, nasal tumors had been found in rats but not in mice, but if the exposure concentrations were to be increased by a factor of 2 or 3, the results may not be negative in mice. He believes that it is too early to draw firm conclusions from this progressing study on nasal cancer from formaldehyde.

Dr. Jess Kraus (University of California at Davis) asked Dr. Alarie the basis of his selection of 0.03 times the RD_{50} as an 8-hr time-weighted average exposure limit to irritant gases or vapors. Dr. Alarie replied that it was a practical compromise in order to keep the average below 10% of the irritant dose. Reduction of the value to 3% was arbitrary. Dr. Marvin Schneiderman further commented that, because the slope of the RD_{50} values was not unity, TLVs for highly irritant materials would be too high and those for less toxic materials would be too low. Dr. Alarie agreed that this interpretation was correct. In response to a further question on this point by Dr. Joseph Meyer

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(E. R. Squibb and Sons) concerning the range of error in the x-axis of his graph and the effects this could have on the slope, Dr. Alarie agreed that the difference between the observed slope of 0.83 and 1 was perhaps not significant. He indicated that the analysis presented was still preliminary and warranted further statistical and other evaluation.

The discussion then turned to dose-response relationships. Dr. Philip Enterline pointed out that the linear, no-threshold dose response was commonly used by EPA, and he asked Dr. Altshuler which type of relationship he preferred among the models he had discussed. Dr. Altshuler replied that he gives greatest credibility to multistage models. He believes that the EPA approach, using the linear no-threshold dose response, is reasonable and conservative, and it is consistent with the multistage model at low doses. Dr. Enterline continued with the question of extrapolation from high doses, as has been done frequently; Dr. Altshuler defended this procedure on practical grounds because often some decision has to be reached based on very limited data. The latter is not really a scientific issue, but is a practical policy matter.

Dr. Marvin Schneiderman stated that, because of competing risks, the time-to-occurrence of an effect with a relatively long latent period may be quite independent of dose, and he asked Dr. Altshuler to comment. In reply, Dr. Altshuler said that, if you believe the multistage model, the effect of a change of dose is a shift vertically in the response curve, i.e., perpendicular to the time axis. This implies at relatively low response levels that the average time to tumor corrected for premature death does not change with dose. Thus, average or median age to an observed effect is very insensitive to dose and is not a good index of response. Dr. Radford pointed out that animal data frequently do show an effect of dose on cancer latent period, to which Dr. Altshuler responded that animal data are generally obtained at high doses, with large fractions of the animals getting cancers. When most animals develop cancer, the multistage model also implies that the average time is going to decrease. The insensitivity of latent period to dose occurs only in the situation where there is low response and numbers at risk do not change significantly with dose in the course of the experiment.

Dr. Radford asked Dr. Land to comment on interpreting animal data on radiation-induced cancer, applying Altshuler's multistage model, which is quite well accepted. Experimental animals are not exposed to the many additional environmental factors that can influence carcinogenesis in man. Thus, how would one anticipate that this situation could modify interpretations of the dose-response data in animals compared to man? He indicated that in man, because of the numerous other agents to which people are exposed and which can act as co-carcinogens or cancer promoters, the induction step for cancer may be the primary determinant of a human cancer response, in contrast to the situation with animals. Dr. Land replied that in animal studies the responses are usually to very high exposure levels, whereas in studies of people we are talking about low levels of response, at the most, a tripling or quadrupling of a generally low normal site-specific risk. Animals that are studied for carcinogenesis often have high natural levels of cancer, and he considered that maybe the behavior of the dose response for very high doses does not have much to do with the dose dependence of risk at the low end of the scale.

Dr. Andelman asked about the problem of variability of exposures within a population under epidemiologic study in defining the relevant dose parameters. Dr. Esmen stated that the dose estimation process should not influence the results. If the population has a particular mode of exposure which can be measured, then he said that exposure of the population through that mode has the measured distribution, provided that other routes of exposure are not dominant. But in a case where the exposures from all modes are extremely varied and are all about the same order of magnitude, it is not certain one can really estimate an exposure with any sort of reliability. A good example of this latter case would be if we try to gauge the effect of being exposed to airborne particulates in a large city without being able to measure personal exposures. If exposures at work, at home, or at hobbies cannot be evaluated, then what one is saying is that exposure to some components of the mix of inhaled particles cannot be estimated, perhaps even to within an order of magnitude or more.

Dr. Andelman cited the issue of lead exposure among the general population. Much of the evidence indicates the exposures are probably distributed lognormally. One evidence of this is the distribution of blood levels. In that kind of situation, what does the epidemiologist do to try to study the effects of lead on a population? One should try to find populations that are exposed to specific concentrations, individual by individual, or in a particular case, perhaps the whole population. But this situation is usually not the case. Therefore, how do you deal with this problem in trying to interpret effects in response to such variable doses? Dr. Esmen replied that, if you know the

frequency distribution of the exposures and if you can estimate its parameters, you can have a reasonable answer. The choice of more and more refined techniques would complicate the mathematics, but it is still possible. The main problem is what happens if one really cannot define the distribution of exposures, especially if an unmeasured or unmeasurable one dominates the dose. Dr. Radford pointed out that the fact that the blood lead is lognormally distributed in a population does not necessarily say anything at all about the distribution of exposures. It is more indicative of individual metabolism, either absorption in the GI tract, or excretion by the kidneys or the intestinal tract, rather than a difference in exposure.

Dr. Andelman also asked about the effect on dose response of variable susceptibility among the study population. Dr. Esmen agreed that this was a further complication added to that of the dose distribution. Dr. Altshuler indicated that for these distributional problems one can take the linear approach according to which the effects are additive. The median should not be used, as is usually done with a lognormal distribution. Use of the average, which is relatively simple to calculate as a first order of approximation, should be sufficiently precise for epidemiologic studies. Dr. Philip J. Walsh (Oak Ridge National Laboratory) stated that if the linear no-threshold hypothesis is used, and there is a wide distribution of exposures, those exposed to higher doses have a higher probability of contracting a disease. Use of average exposure estimates will therefore overestimate risk, because the effective dose will be underestimated. Dr. Altshuler replied that he thought that the difficulty in the extrapolation problem is that, in general, one does not know enough about the true dose-response relationship to determine what is happening at high dose and what is happening at very low dose. He added that observed data at very low doses for estimation of low dose effects are needed. One has to continue to work with biologically plausible theories.

Dr. Radford commented that previous statements suggested that the Druckrey hypothesis did not apply to low doses. According to this hypothesis, if the dose is low enough, then the latent period is so long that it is longer than the life-span of the species, and therefore there is a "true threshold." According to earlier statements that argument is not generally valid. Dr. Altshuler replied that that was a glib dismissal of the real problem. The distributions of latent periods and sensitivity all have tails and none of the tails go out beyond the life of the animal species unless you build into the theory, as an unproven assumption, that there are individual thresholds representing limited susceptibilities and these thresholds extend indefinitely as dose approaches zero. He believed there are no data to support this idea.

Dr. Land commented that, for radiation-induced breast cancer or lung cancers, when you look at groups exposed to high enough doses, where the relative risk is greater than two or three, the distribution of excess cancers over time following exposure to radiation appears to be the same as the distribution over time of cancers not caused by radiation. This result suggests that, at these dose levels, there is not any dependence of latent period on dose. In the case of radiation-induced leukemia, among heavily exposed persons, leukemias tended to occur earlier than those among lightly exposed persons, just because more of them were radiation-caused. The temporal distribution of the naturally occurring cancers corresponded to the natural age-specific rates for leukemia. It is possible to study the latent periods of radiation-induced cancers because there are groups under study of persons who received exposures at a particular time, such as the Japanese A-bomb survivors. He indicated that it seemed significant that from these data there does not seem to be evidence of a relationship between dose and latent period.

Dr. Schneiderman commented that, if the carcinogenic process requires another latent phenomenon in the multistage process and the latent-stage phenomenon is age-related and genetically controlled as the final trigger, then one would find precisely the effect Dr. Land reported in human populations. That is, the distribution of the genetically triggered age-related phenomenon will occur at the same age no matter what the initiating effect was. Animal populations with which we work are artificial populations. They are kept alive as populations because we keep them alive. These are not animals that have responded to particular evolutionary pressures for survival; in fact, the evolutionary pressure would be to wipe out the strain. What is peculiar about these artificial animal populations is that this genetically driven age-related, last-stage phenomenon may come very early in their lives. Thus, the whole process becomes complicated because we should think of some genetically driven promotional effect on cancer induction. All we have been talking about so far have been initiating effects, which are not genetically driven.

Dr. Newell added that what Dr. Schneiderman way saying could also be thought of in terms of the fact that animal studies for the most part are always done with carefully bred and homogeneous populations as opposed to the people in the room

who are very heterogeneous. He also raised the question of whether DNA repair capabilities of man and of experimental animals are very different. For example, for aflatoxins the trout is one of the most sensitive animals in developing massive liver tumors at exposure to low levels in a short time. In contrast, human groups exposed to aflatoxin seem to die of liver toxicity more than from liver tumors.